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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,594	12/12/2003	Charles L. Brooks	18525/04051	1737

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,594	BROOKS ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 04/19/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending and under examination.

Priority: The instant application was filed December 12, 2003. This application claims priority to provisional application 60/433,370, filed December 13, 2002. The priority date is December 13, 2002.

Specification

The disclosure is objected to because of the following informalities: on pg. 18, section [053], the amino acid group described as having a polar or hydrophobic side group does not have the correct amino acids listed; on pg. 22, section [067], the term "Figur" should be corrected to "Figure." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-18 are drawn to a modified human prolactin molecule wherein the molecule comprises at least one mutation in region i), ii), and/or iii). The specification discloses on pages 16-19 that in some embodiments of the invention, the modified human prolactin molecule comprises at least one deletion, replacement, and/or insertion mutations in region i), ii), and/or iii). The specification discloses working examples of some mutated human prolactin molecules, (p. 66 section [0188]), however, these mutations do not encompass all replacement mutations set forth in claims 1-12. The specification discloses a Δ41-52 human prolactin molecule (ex. 9 of instant application), but it does not address any of the other residues that can be subjected to a deletion mutation as set forth in claims 1 and 13-17. Claims 1 and 18 are drawn to a modified human prolactin molecule wherein the prolactin molecule comprises at least one insertion mutation. The specification discloses on page 19 and 34, that in some embodiments of the invention, the modified human prolactin molecule comprises at least one insertion mutation in region i), ii), and/or iii). This is the only instance where the specification mentions an insertion mutation. Applicants do no disclose anywhere that they have created a modified human prolactin molecule with an insertion mutation capable of antagonistic activity. In addition, the subject matter of claims 22-26 are also not provided for in the specification and does not reasonably convey that Applicants have possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-12, 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is drawn to a modified human prolactin molecule wherein the replacement amino acid is an amino acid having a polar or hydrophobic side group chosen from A, V, L, I, P, F, and M. The amino acids A, V, L, I, P, F, and M are categorized as non-polar amino acids. It is unclear which group the replacement amino acids are drawn from, whether they are from the polar or non-polar group.

Claim 12 recites the limitation "H46A, R48A, and H47F" in the claim. There is insufficient antecedent basis for this limitation in the claim because the replacement amino acids in claim 9 are not drawn to basic amino acids, but rather to polar amino acids. In addition, the mutant labeled as H47F does not correspond to the amino acid sequence as depicted as SEQ ID NO.:1, in claim 1. According to SEQ ID NO.:1, the amino acid at residue 47 is Glycine, not Histidine.

Claim 19 is drawn to a modified human prolactin molecule that has greatly diminished binding through site 2. It is unclear what constitutes greatly diminished binding and the degree of binding described by "greatly."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 9, 11, are rejected under 35 U.S.C. 102(b) as being anticipated by Kinet et al. (Kinet et al., (1996) J. Biol. Chem. 271(24): 14353-14360). Kinet et al. teach a human prolactin molecule that is mutated at selected amino acid positions in helices 1 and 4. In Table I, Kinet et al. disclose a list of human prolactin mutants, including Y169A and H173A (p. 14355 table I; claims 1, 2, 9, 11).

Claim 11 is included in this rejection because it is uncertain whether the mistake in the claim is in "polar, hydrophobic" side group or in the specific amino acids listed. If claim 11 is indeed drawn to amino acids A, V, L, I, P, F, and M, then it will be rejected under 35 U.S.C. 102(b) as being anticipated by Kinet et al.

Claims 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Goffin et al. (Goffin et al. (1994) J. Biol. Chem. 269(61): 32598-32608). Goffin et al. teach modified prolactin molecules that exhibit antagonist activity, binds to prolactin receptor

through site 1, has reduced binding through site 2, and exhibits less than 1% of unmodified prolactin's agonist activity. Goffin et al. made human prolactin mutants by oligonucleotide-directed mutagenesis, including A22W, L25R, L25W, and G129R. To estimate the bioactivity of the hPRL mutants, Goffin et al. measured the ability of the mutants to stimulate proliferation of rat lymphoma Nb2 cells, whose growth is lactogen-dependent. The mitogenic effect of each mutant analog on Nb2 cells (Fig. 5B) and its binding affinity for the Nb2 receptor were measured (Fig. 5A). Averaged over three experiments, the IC_{50} ratio (native versus mutant value) for the binding affinities for the mutant analogs were much lower: 0.33 +/- 0.11% (A22W), (p. 32602 biological analysis; claims 19-21). The mitogenic activity of the prolactin mutant analogs were also greatly altered and were 2 to 3 orders of magnitude lower than for native hPRL: 0.217 +/- 0.11% (A22W), (p. 23602 biological analysis; claims 19-21). To investigate antagonistic properties of the W/R mutant prolactin hormones, Goffin et al. measured the mutants' ability to inhibit native hPRL-stimulated Nb2 cell growth. Goffin et al. show A22W and S26W mutant analogs present at concentrations ranging from 0.1 to 5ng/mL caused cell proliferation to decrease by about 10% (p. 32603 Fig. 6; claims 19-21). Goffin et al. teach mutant human prolactins A22W and G129R have a markedly weakened binding site 2 (Fig. 7A) with strong evidence that suggests sequential binding does occur first through site 1 (p. 32605; claims 19-21).

Claims 1, 13, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 20040127407A1). Chen et al. teach a modified human prolactin molecule with a deletion mutation at G49 (SEQ ID NO:7; claims 1, 13, 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinet et al. (Kinet et al., (1996) J. Biol. Chem. 271(24): 14353-14360) in view of Fuh et al. (Fuh et al., (1995) J. Biol. Chem. 270(22) : 13133-13137). Kinet et al. teach modified prolactin mutants (table 1), Y169A and H173A, that differ in binding and bioactivity when compared with wildtype prolactin. The bioactivity of the human prolactin mutants was estimated by measuring their ability to stimulate growth of lactogen-dependent Nb2 lymphoma cells (p. 14354 Nb2 cell culture and in vitro bioassay). Kinet et al. show that mutants Y169A and H173A have significantly reduced bioactivity and reduced affinity to lactogen (or prolactin receptor; Gorrin et al. (1996) Endocrine Reviews 17(4): 385-410)) receptor (Kinet et al. p. 14357 Fig. 3). Kinet et al. teaches the inhibition of lymphoma cell proliferation by administration of a modified prolactin molecule Y169A or H173A (claim 23).

Fuh et al. (Fuh et al., (1995) J. Biol. Chem. 270(22) : 13133-13137) teach the use of prolactin receptor antagonists to inhibit the growth of breast cancer cell lines. Fuh et al. investigated the effects on four different breast cancer lines, T-47D, MCF-7, BT-474, and SK-BR3. It is known that human prolactin receptors are present in 40-70% of tumor

biopsies and that breast cancer cell lines express 2-10 times more hPRL receptors than normal cells (Fuh et al. p. 13133, intro. & table I). Thus, lactogenic hormones, such as human prolactin, that bind specifically to the human prolactin receptor can stimulate the growth of human breast cancer cell lines (Fuh et al. p. 13133, in view of Shiu, 1985; Manni et al., 1986; Biswas et al., 1987).

It would have been obvious for a person of ordinary skill in the art to administer human prolactin mutants (Kinet et al.) to human breast cancer cells (Fuh et al.). The antagonistic properties of the modified prolactin molecules (Kinet et al.) would have an inhibitory effect on the breast cancer cells because of their reduced bioactivity and binding affinity.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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October 20, 2004

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER